Cell nutriments and motility for mechanobiological bone remodeling in the context of orthodontic periodontal ligament deformation

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A B S T R A C T

Bone remodeling is a complex phenomenon during which old and new bone is continuously removed and re-placed. This phenomenon involves several processes at different length scales such as mechanical, biological, molecular, and chemicals. In the current work, we study the influence of the biological (cells) and molecular (oxygen and glucose) factors coupled with mechanical loads in order to predict bone remodeling for orthodontic treatments. A coupled theoretical mechanobiological model is proposed to extract the oxygen variation due to the deformation of the periodontal ligament leading to cell differentiation and activation. The mechan-obiological stimulus is then calculated. The model is applied on a simplified two dimensional geometry to highlight the density variations and migrations of cells and molecular factors influencing the bone remodeling process.

Keywords:
Stimulus
Bone remodeling
Oxygen
Glucose
Cell motility
Periodontal ligament

1. Introduction

Bone is a continually renewed living material [1]. It undergoes continual adaptation under externally applied mechanical loads as initially phenomenologically modeled by Wolff under the well-known Wolff's Law [2]. Many multiscale and/or multiphysics theoretical and numerical models have followed since predicting of the global kinetics of bone remodeling was tried [3–14]. However, there are still many difficulties to obtain a precise understanding of the mechanotransduction processes driving this bone remodeling [15]. For example, bone density evolution is highly dependent on vascularization and nutrient supply [16–18], is difficult to comprehend due to its highly heterogeneous structure [19–23], and depends strongly on the biology distribution and activation processes inside its porous matrix [24–27].

We present here this influence for an application of the mechanobiological couplings in orthodontic bone remodeling due the applied orthodontic forces [28,29]. The cell proliferation is activated through oxygen variation in the periodontal ligament [30–33] being partially occluded due to the applied mechanical forces. We study the variations in the supply chain of nutrients and oxygen to predict cell recruitment, proliferation and migration assuming that bone remodeling occurs by the osteoblasts proliferating with oxygen increase [30] and bone resorption occurs by the osteoclasts proliferating in hypoxia [31,32].

2. Model development

Bone remodeling comes via the application of a mechanobiological stimulus ΔS, defined from a variation of the mechanobiological equilibrium [8,12,14] and newly expressed [18] as:

$$\Delta S = \prod_{i=1}^{n} \int_{\Omega} \alpha_i S_i \exp(-D_i \|\chi(X) - \chi(X_0)\|) dX_0 \quad (1)$$

where n is the total number of external sources S_i (mechanical, biological, electrical, neurological, …) involved in the remodeling process and α_i are their weighting coefficients, triggered by genetic and/or epigenetic factors, allowing to simultaneously control their impact on the overall response of the system as well as their interactions. $\chi(X)$ and $\chi(X_0)$ are the kinematical fields that associate to any material point its current (X) and reference (X_0) position respectively, and D_i is a characteristic distance accounting for each independent effect. The external sources S_i considered in this work are: (i) the mechanical energy accounting for the mechanical loads sustained by the bone cells and triggering bone density evolution, (ii) the concentration of cell nutriments (here being oxygen and glucose) expressed as function of the hydrostatic pressure in specific regions of the system, and (iii) the cells activity triggered by specific levels of oxygen and glucose concentration together with the intensity of the mechanical force applied. The cells recruiting and migration are described via two diffusion

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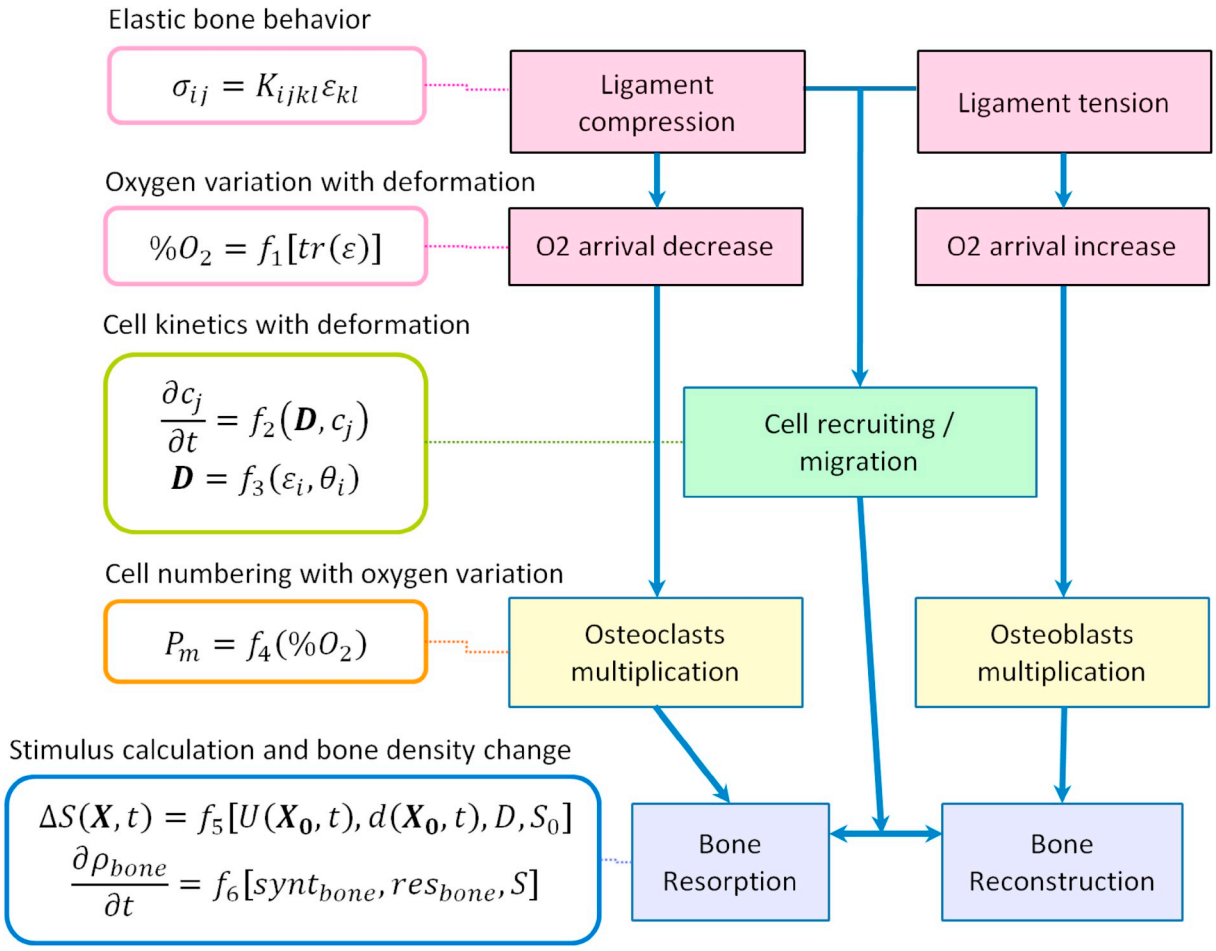

Fig. 1. Schematic of the stepped mechanobiological couplings leading to bone remodeling.

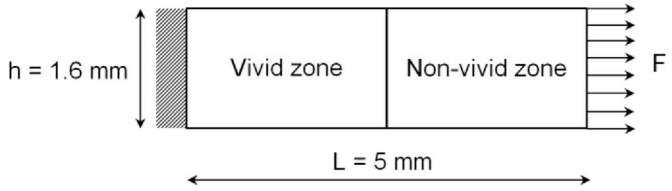

Fig. 2. Schematic of the 2D model used to obtain the cells and molecular migration kinetics.

Table 1
Initial cells and molecular distributions inside the geometry.

	Osteoclasts concentration (%)	Osteoblasts concentration (%)	Oxygen concentration (%)	Glucose concentration (%)
Vivid zone	5	10	20	10
Non-vivid zone	0			

equations [25,33] reading:

$$\frac{\partial c_j}{\partial t} = div\ \boldsymbol{D}\nabla c_j + \alpha_j(1 - c_j)c_j - \beta_j c_j \tag{2}$$

$$\boldsymbol{D} = \lambda_j \boldsymbol{I} + \phi_j \cdot \sum_{i=1}^{3} \in_i \theta_i \otimes \theta_i \tag{3}$$

where c_j is the cell density (with j being the osteoblasts or osteoclasts), t is the time, α_j and β_j are two coefficients of proliferation and differentiation respectively. The diffusion tensor $\boldsymbol{D}$ depends on the principal strains ($\in_i$) and strain directions (θ_i) and with λ_j and ϕ_j two coefficients and $\boldsymbol{I}$ the identity matrix. The bone density variation in time is calculated by the rates of bone synthesis and resorption respectively, depending on the positiveness of the defined mechanobiological stimulus.

The chosen application proposes to solve the mechanobiological effects through a stepped analysis of coupled partial differential equations as presented in Fig. 1.

The presented schematic shows that the applied mechanical force leads to a partial compression or tension of the periodontal ligament. Through elastic mechanical behavior, a variation of oxygen concentration is observed due to blood flow variation inside the periodontal ligament vascularization, which has a direct impact on the osteoblasts [30] or osteoclasts [31,32] concentration. In parallel, compression (resp. tension) of the periodontal ligament influences cells recruiting and migration [33]. The mechanical effect, together with the cellular combined effects, will then impact the calculated mechanobiological stimulus driving the bone density variation.

The proposed schematic of Fig. 1 was implemented in a simplified 2D finite element (FE) numerical model of the periodontal ligament to predict cell density variation and, sugar and glucose concentration variations. As the periodontal ligament is very thin, a simply strained 2D rectangular geometry can highlight the corresponding kinetics (see Fig. 2).

The geometry is anchored on the left side and distributed force is applied on the right side. Biology that is initially distributed on the left side only (vivid zone) will migrate towards the right side (initially non-vivid zone). The challenge to obtain a satisfactory prediction in the bone remodeling process lies in the adequate identification and importance of each of the external sources and parameters used together

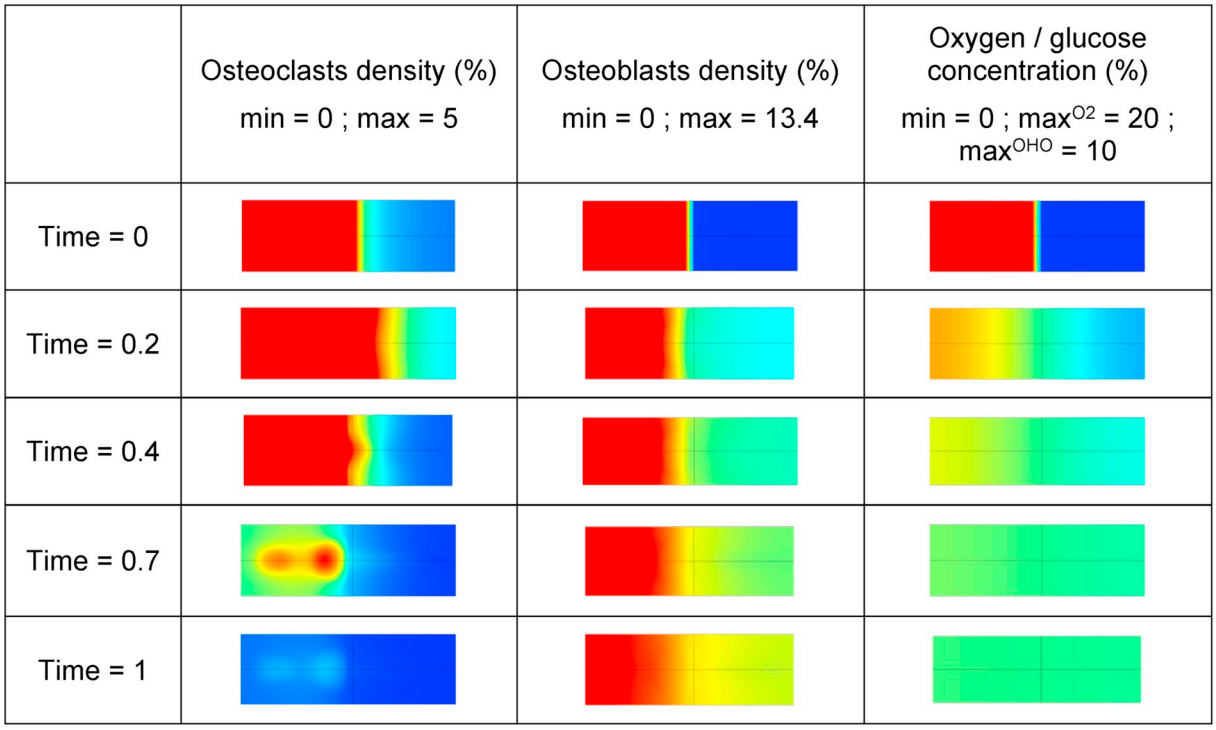

Fig. 3. Evolution of the cells, oxygen and glucose concentration as a function of time.

with their mutual interactions and quantification of each of the applied individual kinetics involved in the process.

3. Results and discussion

The defined model being a strained simplified geometry under simple tension mechanical load, the expected results are the kinetics and extract cells and molecular migration between the two sides of the geometry. The initial parameters distributions are defined in Table 1.

Preliminary results are presented in Fig. 3 for the cells density and molecular evolutions as a function of time (defined arbitrary between 0 and 1).

For osteoclasts, only apoptosis and migration is taken into account, no proliferation. For osteoblasts, proliferation comes from osteoclasts differentiation in addition to migration. Finally, molecular (oxygen and glucose) absolute quantities are not supposed changing, only migrating geographically as a function of time and depending on the applied strain.

Overall, the results show migrations between the small strained (left) and large strained (right) area for each parameter. For osteoclasts, as no proliferation is defined, an initial migration (mid-length) is observed at the beginning of the analysis. But differentiation between osteoclasts to osteoblasts becomes then predominant and osteoclasts density degrades quickly to reach almost zero at the end of analysis. For osteoclasts, both migration and proliferation are observed since the start of the analysis. The maximum density reaches a value of 13.4% (left) then migration become predominant as no more osteoclasts are present to be differentiated and osteoblasts density increases more on the large strained region (right) than on the small strained one (left). Finally, both kinetics of oxygen and glucose being defined identical, the migration between the two regions is completely symmetrical and reaches equilibrium at the end of the analysis since it is supposed not being influenced by other parameters in this model.

Evolutions of these four densities (osteoblasts, osteoclasts, oxygen and glucose) impact directly the mechanobiological stimulus. More specifically, the bone remodeling process will be concentrated where these densities will be the highest at any given time of evolution. It is therefore crucial to know their distributions as it will help to predict the bone density evolution and remodeling process.

4. Conclusion

We presented a coupled multiphysic theoretical numerical analysis integrating the mechanical and biological phenomena within a single mechanobiological stimulus influencing the bone density evolution and remodeling process. This coupled model could help predict the bone remodeling for patient specific orthodontic applications and the orthodontist understanding and optimization of the procedure to follow for each patient's case.

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